COR ET VASA 57 (2015) e270–e274

Available online at www.sciencedirect.com

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journal homepage: http://www.elsevier.com/locate/crvasa

Review article

Comparison of ESC Guidelines 2008 and 2014 – Diagnostic and treatment of acute pulmonary embolism

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ARTICLE INFO

Article history:
Received 5 May 2015
Accepted 18 May 2015
Available online 11 June 2015

Keywords:
Venous thromboembolism
Pulmonary embolism
Diagnosis
Treatment
Guidelines comparison

ABSTRACT

The new revised ESC Guidelines focussing on clinical management of pulmonary embolism has been published in 2014 October issue of EHJ, and it represents current knowledge in respect of optimal diagnosis, assessment and treatment of patients with PE. Czech Society of Cardiology prepared shortened version of the new guidelines, which is published in this issue of Cor et Vasa. In our manuscript we focussed on the most important differences between these two guidelines: Recently identified predisposing factors for venous thromboembolism, simplification of clinical prediction rules, age-adjusted D-dimer cut-offs, subsegmental pulmonary embolism, incidental, clinically unsuspected pulmonary embolism, advanced risk stratification of intermediate-risk pulmonary embolism, initiation of treatment with vitamin K antagonists, treatment and secondary prophylaxis of venous thromboembolism with the new direct oral anticoagulants, efficacy and safety of reperfusion treatment for patients at intermediate risk, early discharge and home (outpatient) treatment of pulmonary embolism, current diagnosis and treatment of chronic thromboembolic pulmonary hypertension and finally, formal recommendations for the management of pulmonary embolism in pregnancy and of pulmonary embolism in patients with cancer.

Contents

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http://dx.doi.org/10.1016/j.crvasa.2015.05.013
0010-8650/

Introduction

Venous thromboembolism (VTE) is the third most frequent cardiovascular disease with an overall annual incidence of 100–200 per 100 000 inhabitants. PE is associated with significant morbidity and mortality. From all the patients suffering PE as many as 15% will die within the first month and of those who do survive, 30% will develop recurrent PE over the following 10 years. Of those who died, only 7% were correctly diagnosed during life.

The new revised ESC Guidelines focussing on clinical management of pulmonary embolism has been published in 2014 October issue of EHJ [1], and it represents current knowledge in respect of optimal diagnosis, assessment and treatment of patients with PE. This version is update of previous guidelines published in 2008 [2]. Czech Society of Cardiology prepared shortened version of the new guidelines, which is published in this issue of Cor et Vasa [3]. Therefore, in our article we focussed only on the most clinically relevant new aspects of 2014-updated version as compared with its previous version published in 2008.

This update is the most comprehensive set of guidelines yet in the field of acute pulmonary embolism (PE). They include 48 pages with 474 references, more than a dozen tables, and about half-dozen figures, plus an appendix of extra tables, available on the website.

The most clinically relevant new aspects in current version relate to following issues:

(1) Recently identified predisposing factors for venous thromboembolism
(2) Simplification of clinical prediction rules
(3) Age-adjusted D-dimer cut-offs
(4) Sub-segmental pulmonary embolism
(5) Incidental, clinically unsuspected pulmonary embolism
(6) Advanced risk stratification of intermediate-risk pulmonary embolism
(7) Initiation of treatment with vitamin K antagonists
(8) Treatment and secondary prophylaxis of venous thromboembolism with the new direct oral anticoagulants
(9) Efficacy and safety of reperfusion treatment for patients at intermediate risk
(10) Early discharge and home (outpatient) treatment of pulmonary embolism
(11) Current diagnosis and treatment of chronic thromboembolic pulmonary hypertension
(12) Formal recommendations for the management of pulmonary embolism in pregnancy and of pulmonary embolism in patients with cancer.

These new aspects have been integrated into previous knowledge to suggest optimal and whenever possible objectively validated management strategies for patients with suspected or confirmed pulmonary embolism. In this article we stressed main differences present between 2008 and 2014 ESC Guidelines.

Risk factors for VTE

Among predisposing factors for VTE with high risk (odds ratio >10) are several new factors: hospitalization for heart failure or atrial fibrillation (within previous 3 months), myocardial infarction (within previous 3 months) and previous venous thromboembolism. New moderate risk factors (odds ratio 2–9) are auto-immune diseases, blood transfusion, erythropoiesis-stimulating agents, *in vitro* fertilization, infections (specifically pneumonia, urinary tract infection, and HIV), inflammatory bowel disease and superficial vein thrombosis. Finally, new weak risk factors (odds ratio <2) are diabetes mellitus and hypertension.

Diagnosis

Clinical presentation

PE may escape prompt diagnosis since clinical signs and symptoms are non-specific.

The authors of the ESC Guidelines 2014 stress the non-specificity of the following symptoms: dyspnoea, pleuritic chest pain, cough, substernal chest pain, fever, haemoptysis, syncope, and signs of DVT (unilateral leg pain). From these only pleuritic chest pain, haemoptysis, and signs of DVT (unilateral leg pain) are somewhat more frequent in patients with PE.

According to the both guidelines (2008 and 2014) suspected acute PE may be divided into two groups: (a) with shock or hypotension – high risk group and (b) without shock or hypotension – non-high risk group. Later in the text of new guidelines you may find classification into four groups, based on early mortality risk – (a) high risk, (b) intermediate – high risk, (c) intermediate – low risk and (d) low risk groups. Risk is estimated according to presence or absence of the shock or hypotension, PESI class, signs of RV dysfunction and laboratory markers (troponin and BNP).

Assessment of clinical probability

Clinical prediction rules in both texts include Wells and Geneva score; new guidelines include also simplified versions of both Wells and Geneva score (see section ''Diagnosis'').

D-Dimer testing

The new ESC Guidelines stresses decreasing specificity of D-dimer in suspected PE with age to almost 10% in patients >80 years. The new guidelines bring also the diagnostic yield of various D-dimer assays in excluding acute PE according to outcome studies, concentrating on the following D-dimer assays: Vidas Exclusion, SimpliRed and Tinaquant.

Imaging methods

Imaging methods are presented in a changed sequence, new guidelines starts with description of value of CT pulmonary angiography, followed by lung scintigraphy, pulmonary angiography, magnetic resonance angiography, echocardiography and compression venous ultrasonography.

Multi-detector CT pulmonary angiography is currently method of choice for imaging pulmonary vasculature in patients with suspected PE, as well as lung scintigraphy remains established diagnostic test, preferentially used in patients with lower probability, normal chest X-ray, in young patients, in pregnancy, in patients with strong allergic history, previous contrast-induced anaphylaxis, severe renal failure and in patients with myeloma and paraproteinemia. Recent studies suggest that data acquisition in the tomographic mode in single photon emission computed tomography (SPECT) imaging, with or without low-dose CT may reduce the frequency of non-diagnostic scans. SPECT imaging may even allow the use of automated detection algorithms for PE. According to the authors of the new guidelines large-scale prospective studies are needed to validate these new approaches.

''Classic'' pulmonary angiography is currently used only in patients with catheter directed treatment of acute PE. Magnetic resonance angiography is now tested for safe ruling-out of clinically significant PE (in combination with absence of DVT on CUS).

Position of echocardiography in PE diagnosis and the risk classification of PE remain stable and in situations, when CT angiography is not immediately available, echocardiography should be used without hesitation. Acute PE may lead to RV pressure overload and dysfunction, which are detected by echocardiography, even though echocardiographic criteria for the diagnosis have differed between studies. New echocardiographic parameters of RV function derived from Doppler tissue imaging and wall stress assessment were reported to be affected by the presence of acute PE, but they are not specific and may be normal in PE patients haemodynamically stable (citace 178–181). Lower limb CUS showing a proximal DVT in a patient with clinical suspicion of PE confirms PE. If CUS shows only a distal DVT, further testing should be considered to confirm PE.

Biomarkers

In the new guidelines, biomarkers are referred on in the section dealing with prognostic assessment of patients with PE in the section ''Thrombolytic treatment'', but their values are not needed for PE diagnosis itself. These markers are basically same as in the old guidelines, though they are divided into markers of RV dysfunction, markers of myocardial injury and non-cardiac markers. Quite new is Table 8 on page 18, where authors present prediction of early mortality in acute PE using imaging and laboratory tests based on data from the results of meta-analyses or when not available thereof, of the largest prospective cohort studies [2].

Recommendation for prognostic assessment

Simplified version of PESI – sPESI consists of the following parameters: age 1 point (if age is >80 years), cancer 1 point, chronic heart failure or chronic pulmonary disease 1 point, pulse rate ≥110 b.p.m. 1 point, systolic blood pressure <100 mmHg 1 point, and arterial oxyhaemoglobin saturation <90% 1 point.

Treatment

Treatment of acute PE depends on estimated early mortality risk (see earlier) and in new guidelines has different sections then before:

Haemodynamic and circulatory support

Haemodynamic and circulatory support with new evidence from experiments and case reports, which suggest that extracorporeal cardiorespiratory support can be effective in massive PE.

Anticoagulation

Anticoagulation – first parenteral (enoxaparin, tinzaparin, dalteparin, nadroparin and fondaparinux), second vitamin K antagonists and third new oral anticoagulants (NOACs) (dabigatran, rivaroxaban, apixaban and edoxaban). Detailed summary of new anticoagulation possibilities is provided in Table 11 page 22 in original article of guidelines. Currently the use of NOACs in the treatment of VTE is indicated, because these agents are non-inferior (in terms of efficacy) and possibly safer (particularly in terms of major bleeding) than the standard heparin/vitamin K antagonists regiment. Therefore, the NOACS can be viewed as an alternative to standard treatment.

Thrombolytic treatment

Thrombolytic treatment – in high risk PE (massive pulmonary embolism) approved thrombolytic regimens for PE currently include rtPA, urokinase and streptokinase in accelerated regime. It must be mentioned: (a) the regime of the half dose of rtPA is not included in the treatment strategies (10 mg rtPA as a bolus, and then 40 mg in an 2 h infusion) in spite that in the older subjects (over 75 years) it decreases the number of bleeding complications, (b) urokinase is now not available in the Czech Republic, and (c) streptokinase and urokinase must be used only the accelerated regimen because the number of bleeding complications depends on the duration of thrombolytic treatment – the longer duration means the more frequent bleeding complications. The present recommendation of 2014 ESC Guidelines in patients with intermediate high risk group is to start all patients on anticoagulation treatment and use thrombolytic treatment only in patients who are haemodynamically deteriorating.

Surgical embolectomy

Surgical embolectomy – remains same as before.

Percutaneous catheter-directed treatment

Percutaneous catheter-directed treatment – current interventional options are clearly defined as thrombus fragmentation systems, rheolytic thrombectomy method, suction thrombectomy and rotational thrombectomy. Results of 35 non-randomized studies are presented and are very favourable, with 87% of patients who survived to discharge from the hospital.

Venous filters

Venous filters – in previous version of guidelines mentioned in other part, here it concludes that currently there are no data to support the routine use of venous filters in patients with free-floating thrombus in the proximal veins.

Early discharge and home treatment

Early discharge and home treatment – the crucial issue is to select patients, who are at low risk of an adverse early outcome The sPESI seems to be the most extensively validated score to date. It possesses a high sensitivity for the identification of low-risk PE, but its value for selecting candidates for early discharge has not yet been directly investigated.

The HESTIA criteria comprise a set of clinical parameters that can easily be obtained at the bed-side, however they have not yet been externally validated. In a meta-analysis of 14 (mostly cohort) studies, the pooled incidence of recurrent VTE, major bleeding and total mortality did not differ significantly between outpatients, patients discharged early and those treated as inpatients.

Therapeutic strategies

Therapeutic strategies – summary of treatment in PE with shock or hypotension, without shock or hypotension, similar as it was in previous guidelines with clear algorithms for acute treatment presented in the new version – page 27–29.

Chronic thromboembolic pulmonary hypertension (CTEPH)

Chronic thromboembolic pulmonary hypertension section is described in much more detailed version in the new guidelines. CTEPH has been reported to be a long-term complication of PE, with a reported cumulative incidence of 0.1–9.1% within the first two years after a symptomatic PE event. Thus routine screening for CTEPH after PE is not supported by current evidence; a significant number of CTEPH cases develop in the absence of previous acute PE. Apart from major pulmonary vascular obstruction, the pathophysiology of CTEPH includes a pulmonary microvascular disease, which may be responsible for the poor outcome in some cases of pulmonary endarterectomy. Clinical symptoms and signs are non-specific or absent in early CTEPH, with signs of right heart failure only becoming evident in advanced disease, with a median time of 14 months between onset of symptoms and diagnosis in expert centres. The diagnosis of CTEPH is based on findings obtained after at least 3 months of effective anticoagulation. While MDCT angiography is the investigation of choice for the diagnosis of acute PE, planar V/Q lung scan remains the main first-line imaging modality for CTEPH, as it carries a 96–97% sensitivity and 90–95% specificity for the diagnosis. Pulmonary endarterectomy is the treatment of choice for the disease. In Europe, in-hospital mortality is currently as low as 4.7% in expert centres. The majority of patients experience substantial relief from symptoms and near-normalization of haemodynamics. In contrast to surgical embolectomy for acute pulmonary PE, treatment of CTEPH necessitates a true endarterectomy through the medial layer of the pulmonary arteries, which is performed under deep hypothermia and circulatory arrest. Patients who do not undergo surgery, or suffer from persistent or residual pulmonary hypertension after PEA, face a poor prognosis.

Optimal medical treatment for CTEP consists of life-long anticoagulation, diuretics, and oxygen. Pulmonary microvascular disease in CTEPH has provided a rationale for use of drugs approved for pulmonary arterial hypertension. These drugs may be justified (a) in inoperable patients and (b) in

patients with persistent or residual pulmonary hypertension after PEA, or in the presence of an unacceptable surgical risk–benefit ratio.

Riociguat has received approval for use in symptomatic patients, who have been classified as having inoperable CTEPH by a CTEPH team including at least one experienced surgeon, or have persistent/recurrent CTEPH after surgical treatment.

Pulmonary embolism in pregnancy

Suspicion of PE in pregnancy warrants formal diagnostic assessment with validated methods. D-Dimer measurement may be performed in order to avoid unnecessary irradiation, as a negative result has a similar significance as in non-pregnant patients.

Venous compression ultrasonography may be considered in order to avoid unnecessary irradiation, as a diagnosis of proximal DVT confirms PE. Perfusion scintigraphy may be considered to rule out suspected PE in pregnant women with normal chest X-ray. CT angiography should be considered if the chest X-ray is abnormal or if lung scintigraphy is not readily available. A weight-adjusted dose of LMWH is the recommended therapy during pregnancy in patients without shock or hypotension. New oral anticoagulants are not indicated in pregnancy.

Pulmonary embolism and cancer

The overall risk of VTE in cancer patients is four times greater than in the general population, in patients receiving chemotherapy is the risk even six times higher and 90-fold in the first week after cancer surgery. Malignancy is taken into account in the estimation of clinical probability of PE and is a risk factor for an adverse outcome in acute PE. The worse outcome is due to the increase risk of bleeding during anticoagulation therapy and to the high rate of reoccurrence of VTE. Management of PE in patients with cancer is described in details in the new guidelines. Important is the new information dealing with patients who present with unprovoked PE in whom about 10% will develop cancer within 5–10 years (majority in the first 1–2 years) after diagnosis of acute PE. The search for occult cancer after episode of VTE can be restricted to careful history, physical examination, laboratory tests and a chest X-ray.

Conflict of interest

No conflict of interest.

Ethical statement

No ethical issues involved.

Funding body

None.

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